REMARKS

I. Status of the Claims

Claims 1-5 and 9-25 are pending in the application. Claims 1, 3-5, 9-21 and 23-25 stand rejected under 35 U.S.C. §112. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 3-5, 9-21 and 23-25 stand rejected under the first paragraph of §112 as lacking enablement. According to the examiner, while the claims are enabled for to the extent of protecting a mouse from an organophosphate comprising administering to the mouse an expression construct comprising a promoter linked to a PON1 gene, wherein expression of the PON1 results in detoxification of the organophosphate, does not provide enablement for treatment or protection of a cell or a subject (presumably other than mice). The rejection is again traversed.

A. Standard of Examination

According to MPEP §2164.04, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. Only if an examiner can provide reasons sufficient to create a reasonable doubt as to the accuracy of a particular broad statement put forward by applicant as enabling support for a claim, a rejection under 35 U.S.C. §112, first paragraph can be made. In other words, a specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirement of the first paragraph of

§112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). With that framework in mind, applicants address the examiner's non-enablement position.

B. References Cited as Undercutting Enablement of Gene Therapy Generally

The first argument advanced by the examiner is a general attack against gene therapy. A number of references were cited, including Anderson *et al.* (1998) and Verma *et al.* (1997). Applicants submit that these references, which actually summarize the state of the art ***in preceding years***, are all but irrelevant to the issue of enablement of gene therapy ***for an application claiming benefit of a filing date in 2001***. In this fast-moving field, a reference 3-4 years old is hopelessly outdated. The remaining references cited – Davis, Schmidt-Wolf *et al.* and Stribley *et al.* – were not discussed at all in the action, and thus applicants submit that the examiner failed to meet the initial burden of establishing unpredictability at the time of filing. Again, applicants point out that a cursory review of these latter three references supports enablement of the present invention:

> **Davis[1]:** "Non-viral delivery systems have the potential to create viable pharmaceuticals from nucleic acids .... *In vivo* problems ... are also encountered [but] ... [r]ecent progress ***has been made*** in overcoming these issues" (emphasis added). *See Abstract.*
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> **Schmidt-Wolf *et al.*:** "Clinical gene therapy ***has been therapeutically beneficial*** in some patients with inherited disease, and it ***is expected that similar benefits will be produced*** in patients with other diseases, such as cancer ..." (emphasis added). *See Conclusions.*

Stribley *et al.*: "Concerns about the safety of human gene therapy research are being actively addressed, and remarkable progress in improving DNA transfer ***has been made***. The first treatment success for a genetic disease (severe combined immunodeficiency disease) has been achieved, and ongoing research efforts will eventually yield clinical applications in many spheres of reproductive medicine" (emphasis added). *See Abstract (Conclusions).*

Each of these papers actually ***supports*** the enablement of gene therapy, and does so ***at the time of filing***. Thus, applicants submit that the previously offered "evidence" of record on the enablement of gene therapy general favors applicants' position.

The examiner has "dismissed" applicants' rebuttal, above "argument of counsel" and as not supported by "evidence." How is it, then, that the examiner can point to a reference, characterize it one way, and have ***that*** be evidence, when applicants did precisely the same thing? In contrast to the examiner's characterization of the previous response, applicants submit that they have merely stated facts: (a) gene therapy is a rapidly developing field; (b) Verma and Anderson are dated references; and (c) Schmidt-Wolf, Stribely and Davis actually ***state*** that gene therapy works. Again, hurdles and problems to not mean that gene therapy doesn't work – they simply indicate that these challenges must be addressed. The examiner attempts to bolster his position by citing additional references – Linthout, Thomas, Juengst and Rosenberg. As with the previous office action, absolutely ***no*** attempt is made to cite relevant portions of these references, and as such, applicants do not believe they have any obligation to engage in a debate regarding their content – the examiner has a greater burden in advancing/maintaining a rejection than to

[1] It should be noted that this reference addresses ***non-viral*** delivery systems. Since applicants have elected the species of adenoviral delivery, it seems that an attack on non-viral delivery systems is premature until such time as the election of species requirement is withdrawn.

simply say "see the reference." ***THAT*** is an example of "arguments ... [that] cannot take the place of evidence of record."

However, in order to complete the record, applicants provide the following citations from each reference:

> **Linthout *et al.*:** "In summary, (adenoviral" gene transfer of cytoprotective gene has been shown to be beneficial to transplanted islet survival." *See p. 2931;* . "Adenoviral gene transfer of hepatocyte growth factor 'HGF' has been shown not only to improve β-cell proliferation, but also to enhance β-cell function." *See p. 2395; see also Table 2, showing various systems, advantages, disadvantages* ***and solutions***.
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> **Thomas *et al.*:** "Our findings have allowed us to develop vectors with improved efficiency, specificity and safety, and some clinical successes have recently been achieved." *See p. 346.* "We have encountered many obstacles so far, and will probably encounter more, but these obstacles are not insurmountable." *See p. 356.*

With regarding to Juengst and Rosenberg & Schechter these are editorials, are not peer-reviewed, and hence do not represent a consensus view of the field. As such, they are entirely inappropriate to establish anything regarding what the skilled artisan might believe about gene therapy.

Further, the examiner ponders "it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed expression cassettes generates a therapeutic effect." It should be pointed out that, in point of fact, a "therapeutic effect" is not claimed. What is claimed is detoxification. If the examiner is concerned about ***which*** constructs can achieve this, a simple *in vitro* assay will identify those that are capable of expressing PON1. Thus, one need not, as the examiner seems to suggest, prove up each embodiment by conducting

clinical trials with multiple vectors in multiple animal subjects (*e.g.*, dogs, cats, mice, humans) in order to enable the present claims.

In response, the examiner seems to generally disagree, citing case law to the effect that "everything within the scope of the claim [must be] enabled." This paraphrasing of the case law is liberal, at best, and outright false at its worst.[2] Indeed, earlier (and unchallenged) case law states that "the scope of enablement must only bear a 'reasonable correlation" to the scope of the claims." MPEP §2164.08, citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Indeed, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. MPEP §2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Finally, the examiner comments that "the claimed method embraces future protection of a cell or a subject from an organophosphate toxin." What is meant by this statement is not clear, but clearly such a reading of the claim in not supported literally or in light of the specification.

Applicants would further submit that nothing in this aspect of the rejection addresses the ***claimed*** invention. Rather, it seems primarily to cast dispersions on gene therapy as a general matter (indeed, the outdated Verma *et al.* and Anderson papers do ***precisely*** this). Yet by now, it cannot be argued that gene therapy *per se* is not enabled. The PTO has issued dozens (if not hundreds) of gene therapy patents, and there are hundreds of gene therapy clinical trials going on around the world, including many that have shown clinical benefit (see quote above from

Schmidt-Wolf *et al.*). Thus, to start out with the default position of "gene therapy is *per se* not enabled" is factually incorrect. And it is ***not*** sufficient, as a response to this argument, for the PTO to say that "each application is examined on its own merits, and there is no evidence showing efficacy of the ***claimed*** invention" – this is for the simple reason that the PTO is using the alleged deficiencies of ***other*** (and much older) gene therapies to support the present rejection. If the PTO is going to advance ***generalized*** concerns regarding gene therapy, then it must be prepared to consider and address ***generalized*** rebuttals thereof.

The examiner argues, in response, that "there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the claimed gene therapy." Of course, this simply truism is ***not*** applicants' point at all. What ***is*** applicants' point is that the examiner's *per se* position that gene therapy is not enabled is not supported by reality. Many gene therapies indeed work, to some extent, and where no particular level of clinical benefit is claimed, then it should ***not*** be the PTO's position that applicants must "start from scratch," *i.e.*, re-establish that particular vectors, control sequences, routes of administration, dosing regiments, *etc.*, are capable of use. Rather, the PTO should be looking at ***this*** invention in particular and explaining why a PON1-based gene therapy would ***not*** be expected to work. This has not be done here.

C. Specific Concerns Regarding Enablement

The examiner has addressed the issue of timing, and it is argued that exposure to the toxin may occur over short or long periods of time, the latter creating problems given the alleged transient nature of gene therapy. In addition, it is argued that levels of toxins, such as in chemical warfare, may overwhelm exogenous PON1 expression, and that information of

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[2] Applicants note that this is a direct quote from the MPEP. However, a review of the *AK Steel*

needed/achieved expression levels is not provided. Again, applicants submit that it will ***always*** be possible to imagine extreme scenarios where an invention will not work, for example, conducting the claimed methods on the surface of the sun. This is not the standard for enablement, however; indeed, the question is not whether ***every*** embodiment will work to a maximum conceived benefit, but whether there is a reasonable correlation between that which is claimed and that which reasonably can be achieved.[3]

Here, if there is short-term exposure, then there appears to be little question that vectors can express PON1 short-term, and thus will facilitate protection. If the exposure is long-term, then at least protection will be afforded in the short-term, and re-administration may be effected to achieve longer-term protection. As for overwhelming PON1 expression with high toxin levels, applicants submit that it is not incumbent upon applicants to establish that in each and every scenario complete protection be provided. In fact, applicants submit that even if toxin levels can outstrip PON1 expression, there would at least have been protection for the subject ***until levels of toxins exceed the protective level of PON1***. This still satisfies the limitation of the present claims, which only requires detoxification, not total elimination of a toxic threat. The examiner did not offer ***any*** rebuttal to this line of argument, failing entirely to comment on applicants' previous rebuttal.

D. Mouse Model

Finally, applicants note the examiner's attack on the mouse model described in the examples, and argues that extrapolation to human subjects is not proper. Applicants again disagree with the examiner's reasoning. First, this is not an immunocompromised animal, as is

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decision revealed nothing comparable to the language used by the MPEP.

often used in other disease models such as cancer. Second, this is also a situation where the interplay with an animal's endogenous systems, such as the immune system or cardiovascular system, is not required. The simple question is whether one can express a PON1 gene *in vivo* and have it detoxify an organophosphate toxin. The examiner has not offered any concrete reason why protection afforded by PON1 expressed from an adenovirus in a mouse would not provide *prima facie* evidence that the same vector would provide the same expression and protection in a human. Rather, the rejection again reduces to a generic attack on gene therapy that must, at this late stage, be considered outdated.

The examiner cited a GAO report (now indicating for the first time that page 8 is the relevant part of this 39-page report is relied upon) for the proposition that extrapolation from animals to humans is unpredictable. What this page says about animal models is contained in a single sentence: "Second, the extrapolation of findings from studies on the effects of chemical warfare agent exposures in animals to humans can be imprecise and unpredictable." This statement can hardly be applied against applicants' specific murine model (no reference to mice could be found anywhere in the GAO report). At most, the report concludes that "the literature does not adequately address ... animal-human extrapolation models ...." See GAO Report, page 22. Adequately address ***what***? This is a far cry from establishing non-enablement of the claimed invention, and at most, the report can be said to criticize the use of research animals to determine whether exposures to low level sarin (a nerve agent), below concentrations needed to produce immediate toxic effects, can cause lasting changes in brain structure or function that further cause chronic ill health. This issue does ***not*** address gene therapy, and thus is over limited impact here, where applicants' animal model is based on an entirely different experimental

[3] Applicants refer the examiner to the amended claims. All that is required is detoxification or an

design, namely, whether boosting of PON1 isoenzyme levels in blood protects a mouse from organophosphate toxicity by increasing the rate of destruction of the organophosphate in blood so that it cannot reach brain and other tissues to cause illness. Because this model addresses the destruction of organophosphates in blood ***before*** they get to the brain, it avoids questions of whether and how organophosphates affect tissues once they reach them (the subject addressed by the GAO report).

For three decades it has been established that the main determinant of susceptibility to organophosphate poisoning is the activity level of PON1 isoenzymes, and this relationship has been shown to hold across many species including humans (see of Davies *et al.*, *Nature Genetics* 1996;14:334-336, "interspecies differences in PON1 activity correlate well with observed median lethal dose (LD_{50}) values [of organophophates]" – abstract; citing 3 additional references). It also should be noted that the use of human PON1 genes in the applicants' gene therapy device injected into the mouse model obviated any argument that interspecies variation in PON1 isoenzyme activity clouded the results. Thus, the examiner's objection to extrapolation from applicants' mouse model to humans is directly contradicted by the published literature. This line of argument also went complete unaddressed in the most recent office action.

As discussed in the MPEP, an *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method. "... [I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as

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organophosphate, which by definition protects the subject from that organophosphate molecule.

reasonably correlating to the condition." MPEP §2164.02. This rule, in essence, directs the examiner here to accept applicants' examples as correlative, in the absence of a reason not to. The GAO report, despite the examiner's position, is ***not*** such a reason.

E. Summary

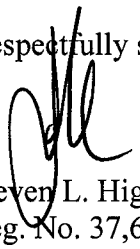
In sum, the examiner's repeated statements that "gene therapy with PON1 has not been attempted" shows that the examiner is approaching the entire enablement issue from a fundamentally ***wrong*** position. The relevant inquiry is whether one of skill in the art believes that gene therapy ***can*** be achieved, not whether or not is ***has*** been achieved. The evidence of record overwhelmingly supports the conclusion that one of skill in the art ***would*** find the present claims enabled. As such applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Please date stamp and return the enclosed postcard as evidence of receipt.

Respectfully submitted,



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Date: November 17, 2006